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Toll-like receptor-mediated innate immunity against herpesviridae infection: a current perspective on viral infection signaling pathways

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Abstract

Background: In the past decades, researchers have demonstrated the critical role of Toll-like receptors (TLRs) in the innate immune system. They recognize viral components and trigger immune signal cascades to subsequently promote the activation of the immune system.

Main body: Herpesviridae family members trigger TLRs to elicit cytokines in the process of infection to activate antiviral innate immune responses in host cells. This review aims to clarify the role of TLRs in the innate immunity defense against herpesviridae, and systematically describes the processes of TLR actions and herpesviridae recognition as well as the signal transduction pathways involved.

Conclusions: Future studies of the interactions between TLRs and herpesviridae infections, especially the subsequent signaling pathways, will not only contribute to the planning of effective antiviral therapies but also provide new molecular targets for the development of antiviral drugs.

Keywords: Herpesviridae, Toll-like receptor, Immune mechanism, Viral infection

Background

Toll-like receptors (TLRs) are a group of single, membrane-spanning, non-catalytic proteins in the immune system that are critical for recognizing structurally-conserved molecules derived from pathogenic microbes. To date, thirteen members have been identified in the TLR family. TLRs 1–10 are found in the human genome, and TLRs 11–13 occur in mice [1–6]. The structures of TLRs and other TLR-ligand complexes have been described [7–15]. Leucine-rich repeats have been described in the variable N-terminal extracellular part of TLRs, and have been shown to bind pathogen-associated molecular patterns, which are broadly shared by pathogens but not the host. This interaction allows the host to discriminate autologous from xenogenous substances [16].

TLRs are mainly expressed on the membranes of immune cells including macrophages, dendritic cells, T cells, and B cells [17–22]. Moreover, TLRs are also found in non-immune cells, such as endothelial and epithelial cells, adipocytes, and cardiomyocytes [23–27]. TLRs predominantly occur on the cell surface, while TLRs 3, 7, 8, and 9 are expressed inside cells [3]. These four TLRs are primarily involved in the identification of xenogenous nucleic acids from invaders. The cellular localizations and ligands of human TLRs 1–9 are listed in Table 1.

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Table 1 Properties of toll-like receptors

TLRs	Localization	Ligands
TLR1/2 [33–35]	Cell surface	Triacylated lipopeptides
TLR2/6 [36–41]	Cell surface	Diacylated lipopeptides (*Mycoplasma*), Lipoteichoic acid (*Streptococcus*), Zymosan (*Saccharomyces cerevisiae*)
TLR2 [38, 42–48]	Cell surface	Peptidoglycan (Gram-positive bacteria), Lipoarabinomannan (Mycobacteria), Hemagglutinin (measles virus), phosphatidylinositol mannoside 6 (Mycobacteria), Glycosylphosphatidylinositol (*Trypanosoma*)
TLR3 [49–52]	Endosome	ssRNA virus (West Nile virus), dsRNA virus (Respiratory syncytial virus, murine cytomegalovirus)
TLR4 [43, 53–59]	Cell surface	Lipopolysaccharide (Gram-negative bacteria), Mannan-binding lectin (*Candida albicans*), glycoinositol- phospholipids (*Trypanosoma cruzi*), Envelope proteins (respiratory syncytial virus, mouse mammary tumor)
TLR5 [60, 61]	Cell surface	Flagellin (flagellated bacteria)
TLR7 [62, 63]	Endosome	ssRNA viruses (vesicular stomatitis virus, influenza virus)
TLR8 [64–66]	Endosome	ssRNA from RNA viruses
TLR9 [67–71]	Endosome	dsRNA viruses (herpes simplex virus, murine cytomegalovirus), CpG motifs from bacteria and viruses, Hemozoin (*Plasmodium*)

Table 2 Properties of the herpesviridae family

Herpesviridae family members	Corresponding TLRs
Herpes simplex virus type 1 (HSV-1) [72–75]	TLR2, TLR3, TLR4, TLR9
HSV-2 [76, 77]	TLR2, TLR3, TLR4, TLR9
Varicella zoster virus [78, 79]	TLR2, TLR3, TLR9
Epstein-Barr virus [80–83]	TLR2, TLR3, TLR7, TLR9
Cytomegalovirus [84, 85]	TLR2, TLR3, TLR4, TLR5, TLR9
Human herpesvirus 6 (HHV-6) [86–89]	TLR4
HHV-7 [86]	TLR2, TLR4
Kaposi's sarcoma-associated herpesvirus [90–93]	TLR3, TLR4, TLR9

The herpesviridae family comprises a large group of enveloped DNA viruses characterized by latent infection in their hosts. Currently, eight family members are known to be associated with widespread human infection (Table 2). Upon detecting members of this family, TLRs recruit adaptor proteins, including myeloid differentiation factor 88 (MyD88), TIR-domain-containing adaptor-inducing interferon-β (TRIF), TIR-domain-containing adaptor protein (TIRAP), and TRIF-related adapter molecule (TRAM). This is followed by signal transmission to activate transcription factors including nuclear factor kappa B (NF-κB), activator protein-1 (AP-1), and interferon regulatory factors (IRF3/7). These factors enter the nucleus, stimulating transcription to promote pro-inflammatory cytokines and interferon (IFN) expression [5, 6, 28]. The inflammatory cascades defend against viruses while also injuring the host. Under physiological conditions, regulatory systems function in the host to inhibit excessive activation of the TLR signaling pathways to maintain homeostasis; these include Annexin A2, the ubiquitin ligase TRIAD3A, RP105, and acetylation of lysine residues [29–32]. Here, we clarify the mechanism underlying the human TLR-mediated innate immune response against herpesviridae in the activation and reactivation of virus infection.

Main text

Herpes simplex virus

Herpes Simplex Virus (HSV) infection is a worldwide cause of severe medical conditions such as encephalitis, keratitis, and neonatal herpes [94, 95]. It has two serotypes, HSV-1 and HSV-2, which primarily infect individuals through epithelial cells. After initial infection, it forms a latent infection in ganglia and latency-associated transcripts are expressed [96]. HSV US3 protein inhibits TLR3 responses in cultured human monocytes [97]. Similarly, HSV immediate-early ICP0 protein suppresses the TLR2-mediated innate immune response and NF-κB signaling [98]. HSV downregulates TLR2 and TLR4 in a THP-1 monocyte cell line [99]. These findings reveal the evasion mechanism of HSV. When host immunity is weak, HSVs begin to reactive to establish infection.

Studies have revealed that TLR2, TLR3, TLR4, and TLR9 are capable of recognizing specific components of HSV such as glycoprotein B (gB), glycoprotein H (gH), glycoprotein K (gK), glycoprotein L (gL), and US2 protein in the activation and reactivation of HSV [100–105]. TLR signaling activates the transcription of immune response genes by inducing the secretion of intracellular protein signaling molecules such as interleukins (ILs) and interferons (IFNs) to protect the host. Furthermore, TLR2 and TLR9 have been shown to synergistically fuel innate immunity to defend against HSV-1 and -2, showing a protective effect [102, 106].

Interactions of HSV with TLR2 and TLR4

Upon invasion of HSV-1 and -2, viral glycoproteins including gH and gL are recognized by TLR2 [107]. TLR2 is located on the dendritic cell surface and

hetero-dimerizes with TLR6 or TLR1 to recognize viral glycoproteins [108]. Once HSV-2 has invaded the host, TLR4 recognizes the short-hairpin DNA from HSV on the cell surface [109]. Villalba et al. reported that TLR2 and TLR4 expression occurs as early as 1 h after HSV-1 infection and increase the levels of IRF3, IRF7, INF-β, and IL-6 [110]. The activation of TLR2 or TLR4 launches the MyD88-dependent signaling cascades and assembles macrophages and natural killer cells [109, 111]. MyD88 recruits IL-1 receptor-associated kinase 1 (IRAK1), then activates tumor necrosis factor receptor-associated factor (TRAF6) [112–115]. Subsequently, transforming growth factor-β-activated protein kinase-1-binding protein-2 (TAB2) and transforming growth factor-β-activated kinase-1 (TAK1) are recruited to stimulate the inhibitor of nuclear factor κB kinase (IKK) complex which comprises IκB kinase α (IKKα), IKKβ, and IKKγ (NEMO) [113, 116, 117]. IKKα serves as a stimulator of NF-κB in the IKK complex. In contrast, IKKβ phosphorylates and degrades the inhibitor of NF-κB (IκB) to release NF-κB [118, 119]. Alternatively, mitogen-activated protein kinases (MAPKs) are triggered by TAK1 to allow AP-1 into the nucleus [120–124]. NF-κB and AP-1 enable immune cells to secrete IL-15, TNF-α, and IFN to defend against HSV and counteract viral absorption. In addition, studies have demonstrated that the expression of chemokines, such as chemokine (C–C motif) ligands 7, 8, and 9, as well as chemokine (C-X-C motif) ligands 1, 2, 4, and 5, which play important roles in the innate immune response against HSV [125, 126]. Surprisingly, when activated via the TLR4-MyD88 axis, AP-1 upregulates TLR4 expression by feedback in genital epithelial cells to enhance immunity in humans [127]. A study has also shown that Sp1 has a significant effect as a major transcription factor involved in TLR2 promoter activity [107, 128].

Moreover, Kurt-Jones et al. demonstrated that neonates produce more pro-inflammatory cytokines than adults, which may explain the sepsis syndrome that is seen with HSV-1 and -2 [129]. This result is in accord with the finding that TLR2-deficient mice are more likely to survive HSV-1 than wild-type mice [105]. Besides the cytokine response, TLR2 signaling generates reactive oxygen species and induces oxidative stress, which cause damage in wild-type microglial cell cultures; but this does not occur in cells from TLR2-deficient mice. The consequences of oxidative stress are associated with reduced activation of the MAPK pathway [130]. These results suggest that the immune response mediated by TLR-2 can be not only beneficial but also detrimental to the host [105]. Surprisingly, TLR2 and TLR9 synergistically activate the innate antiviral response defense against HSV-1 and -2, showing a protective effect [106]. Compared to TLR2, TLR3 seems to have a protective effect [131, 132].

Interactions between HSV and TLR3

Upon identification of invasive HSV-1 and -2, the host cells form endosomes that spontaneously wrap up the virus. Unc-93 homolog B1 (UNC-93B) is a transmembrane protein localized on the endoplasmic reticulum (ER) that transfers TLR3, 7, 8, and 9 from the ER to the endosome [133–136]. Upon HSV-1 and -2 stimulation, TLR3 interacts with UNC-93B1 and shifts from the ER to endosome [134, 135]. In the endosome, TLR3 is phosphorylated by tyrosine kinase c-Src, epidermal growth factor receptor (EGFR), and phosphatidylinositol 3-kinase (PI3K) to form dimeric TLR3, which initiates a downstream signaling pathway. Although a mutual action between HSV RNA and TLR3 has not yet been demonstrated, it is likely that HSV-1 and -2 produce dsRNA that serves as a ligand for TLR3 [137–147]. The activation of TLR3 recruits TRIF and TRAF [148, 149]. TLR3 is the only member of the TLR family that can recruit TRIF and TRAF as the signal transduction factor, instead of MyD88. Upon TRIF recruitment, TANK-binding kinase-1 (TBK1), inhibitor of nuclear factor κB kinase ε (IKKε), NAK-associated protein 1 (NAP1), and TRAF3 constitute a signaling complex that leads to the activation of IRF3/IRF7 and NF-κB [150–157]. The activation of IRF3 and NF-κB induces the production of IFN-β, TNF-α, and IL-6 [158, 159]. Meanwhile, TRAF recruits the downstream protein receptor interacting protein 1 (RIP1), which subsequently recruits TAB2 and TAK1 to form a complex to trigger IKKα and IKKβ [160–162]. These two kinases with the IKK receptor protein IKKγ (NEMO) constitute the IKK complex [163]. IKKα activates downstream NF-κB, while IKKβ phosphorylates the inhibitor of NF-κB (IκB) leading to the degradation of IκB [119, 161]. The complex formed by TAB2 and TAK1 also activates AP-1 via MAPKs [164]. Subsequently, NF-κB, AP-1, and IRF3/IRF7 enter the nucleus and facilitate the release of IFN-β, TNF-α, and IL-6 to defend against HSV [165, 166] (Fig. 1).

Interactions between HSV and TLR9

TLR9 is one of the crucial components in the defense against HSV-1 and -2. Similar to TLR3, TLR9 is stabilized by UNC-93B1 through preventing its degradation and transporting it from the ER to the endosome [136]. This redistribution of TLR9 is associated with cytosine-phosphate-guanine DNA (CpG DNA). Both HSV DNA and CpG oligonucleotides contain abundant CpG motifs [167, 168]. CpG DNA drives TLR9 to shift into early endosomes and CpG oligonucleotides access the endosome. Subsequently, the

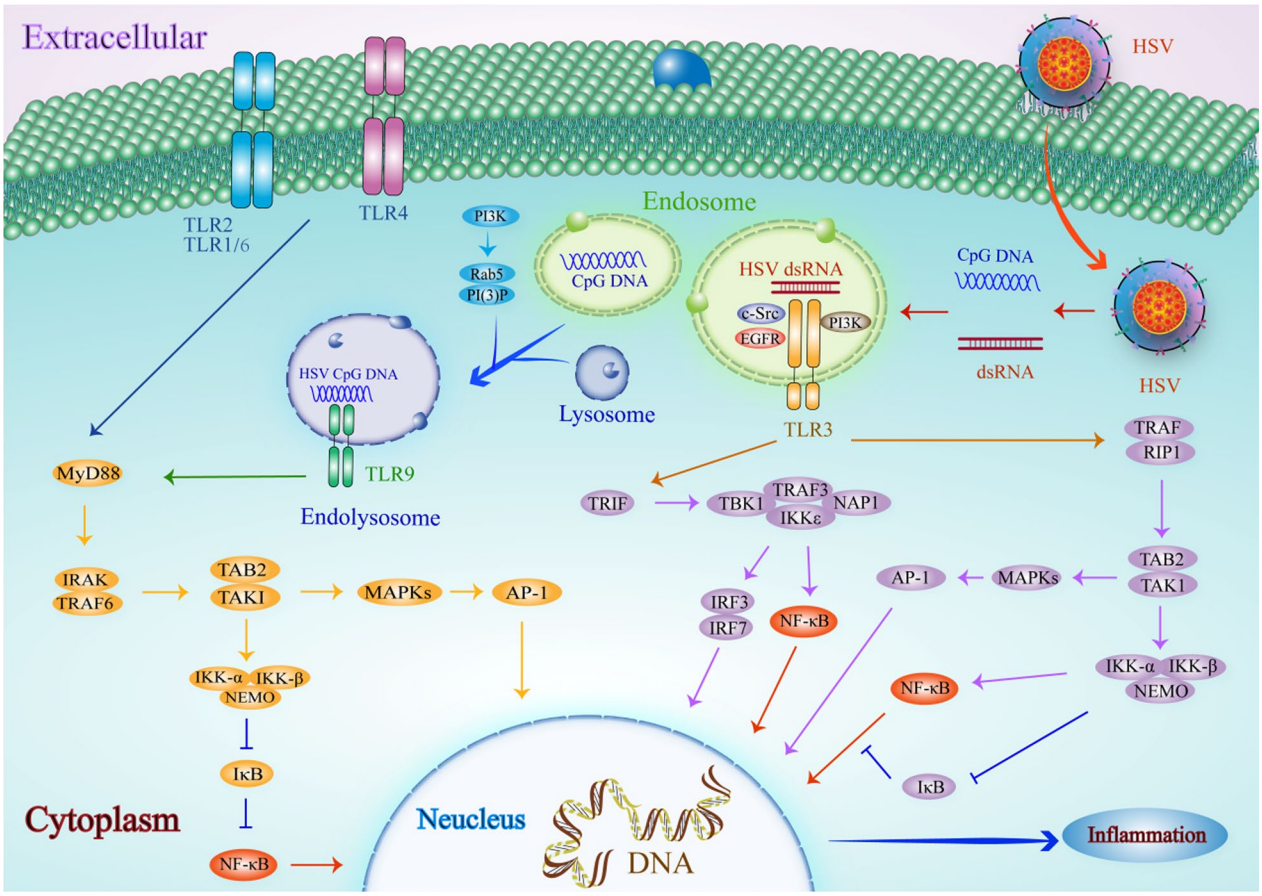

Fig. 1 TLR-mediated signaling pathways in response to HSV**.** Upon HSV ligand stimulation, TLR2, TLR4, and TLR9 recruit the adaptor MyD88. Once recruited, MyD88 binds the protein complex composed of IRAK and TRAF6. TRAF6 results in the phosphorylation of TAK1, which then activates the IKK complex that results in the phosphorylation and degradation of IκB. The degradation of IκB allows NF-κB to translocate into the nucleus. Alternatively, TAK1 activates the MAPK pathway, triggering the activation of AP-1. Under HSV stimulation, TLR3 is localized and phosphorylated by tyrosine kinase c-Src, EGFR, and PI3K in the endosome. Moreover, TLR3 triggers TRIF to enable TBK1, IKKε, NAP1, and TRAF3 to generate a complex. Furthermore, this complex leads to the activation of IRF3/IRF7 and NF-κB. TLR3 recruits TRAF and RIP1 to phosphorylate TAB2 and TAK1. The complex formed by TAB2 and TAK1 activates AP-1 via the MAPK pathway and NF-κB via the IKK complex-IκB pathway. Together, NF-κB, IRF3/IRF7 and AP-1 induce the expression of inflammatory cytokines to protect the host by innate immunity

oligonucleotides assemble and form a secondary structure near the core CpG motif to activate TLR9 [3, 169, 170]. Guanosine triphosphatases (Rab GTPases) mediate the maturation of endosomes. Upon maturation, endosomes that contain CpG DNA combine with lysosomes. The hallmark of the maturation of endosomes involves the formation of endolysosomes [171–173]. On the endosomal membrane, Rab5 mediates class III phosphatidylinositol-3 kinase to produce phosphatidylinositol-3 phosphate that interacts with Rab5 to regulate and promote the maturation of early endosomes [174–176]. Furthermore, MyD88 activates IRAK1/4 to trigger the protein TRAF6. Subsequently, TRAF6 recruits and activates TAK1 (transforming growth factor-β-activated kinase 1) through the K-63-linked poly-ubiquitination of TAK1 and TRAF6 [177–179]. TAK1 initiates downstream cascades, including MAPKs and the NF-κB-inducing kinase (NIK)-IKK-IκB signaling pathway [180, 181]. In this pathway, NF-κB is isolated and inactivated in the cytoplasm primarily by IκB. The proteolysis of IκB is regulated by the activation of IKKs including IKKα, IKKβ, and IKKγ [182, 183]. Activated IKKβ leads to the phosphorylation and proteolysis of IκB [182]. NF-κB is unlocked and subsequently enters the nucleus. These processes induce the activation of transcription factors such as AP-l and NF-κB, directly facilitating the downstream gene expression of IL-10, IL-12, TNF-α, and IFN-β [180, 184–186] (Fig. 1).

Varicella zoster virus

Varicella zoster virus (VZV) causes chicken-pox in the primary infection. In elderly or immunosuppressed patients, reactive VZV can cause herpes zoster after latency [187]. During the latency, VZV downregulates the surface expression of the NKG2D ligands of ULBP2 and ULBP3, which reduce the activation of natural killer cells in the presence of VZV [188].

Studies have reported that TLR2, TLR3, and TLR9 play crucial roles in the activation and reactivation of VZV [189–191]. TLR9 induces plasmacytoid dendritic cells (pDCs) to secrete IFN-α via the MyD88 signaling pathway involved in infection by VZV [191]. In addition, VZV triggers monocytes and macrophages to produce NF-κB via TLR2 and allows the secretion of the antiviral factor IL-6, but TLR2, TLR3, and TLR4 are not involved in the IFN-α production induced by VZV infection [189, 192]. Besides, studies have demonstrated that TLR3 is involved in the recognition of VZV [193]. There is no evidence that the expression of TLRs on non-immune cells react to infection with VZV. However, unlike other herpesviruses, the cytokine response to VZV is species-specific. VZV does not induce cytokines in mouse embryonic fibroblasts or in a mouse cell line, but it does trigger NF-κB in a human cell line expressing a mouse TLR2 construct [189].

Epstein-Barr virus

Interactions of EBV with TLR2

Epstein-Barr virus (EBV/HHV-4) is primarily transmitted via saliva. It proliferates in oropharyngeal epithelial cells, infects B lymphocytes, and enters the bloodstream to cause systemic infection. During the latency, the EBV lytic protein BGLF5 targets TLR9 mRNA for degradation in EBV-infected B cells, reducing the function of TLR9 [194]. Moreover, BGLF5 also targets TLR2 in infected cells [195]. In addition, a late lytic tegument protein, BPLF1, prevents TLR-mediated IFN production [196]. Besides, EBV-encoded miRNAs inhibit the TLR signaling pathway [197].

In the activation and reactivation of EBV, a membrane receptor expressed on the surface of B lymphocytes, TLR2 unites with TLR1 or TLR6 to form a hetero-dimer, which combines with lipoproteins or lipopeptides to serve as an active signaling complex. The TLR heterodimer (TLR2/TLRx) is the key to recognizing EBV. Eric Gaudreault et al. found that infectious and UV-inactivated EBV induce NF-κB activation and the secretion of primary monocyte chemotactic protein in a TLR2-dependent manner [198]. TLR2 activation initiates the MyD88-dependent signaling cascades. MyD88 recruits IRAKs, including IRAK1 and IRAK4, which stimulate TRAF6 and phosphorylate IKK, IκB, and NF-κB [199].

Interactions of EBV with TLR3

When EBV penetrates a cell, it transcribes small non-coding RNAs called EBERs by using the host RNA polymerase III, and TLR3 is activated in the ER. EBERs induce inflammatory responses through TLR3 and neural precursor cells, resulting in high levels of cytokines such as TNF-α and IL-6. In addition to acting as an inflammatory mediator, NF-κB is capable of upregulating the expression of EBERs and LMP1 (EBV latent membrane protein 1), thereby triggering moderate inflammation [200, 201]. EBERs promote LMP1 transcription through NF-κB. Conversely, MP1 also stimulates NF-κB to increase the expression of EBERs. This positive regulatory loop becomes a necessary driving force for the inflammatory–carcinogenic transformation of EBV-infected epithelial cells.

Interactions of EBV with TLR7

Furthermore, the EBV genome encodes two membrane proteins, LMP1 and LMP2, that act as natural signals of B-cell activation. LMP1 and LMP2 are required for the interaction of the ligand with the CD40 receptor and B-cell receptor. Martin et al. found that the TLR signaling pathway is a third pathway for activated B lymphocytes [202]. They reported that, after EBV infection of B lymphocytes, EBV gene expression transcribes ssRNA that stimulates TLR7 signaling, resulting in up-regulation of the TLR7 and MyD88 genes to activate IRF-5 and IRF-7 [203]. IRF-5 and NF-κB synergistically trigger cytokine promoters to induce the production of inflammatory cytokines. Moreover, they also provide a signal equivalent to the CD40 ligand to promote B cell activation and expansion in the initial phase of EBV infection. Therefore, it has been suggested that, in the early stage of infection, EBV stimulates TLR7 signaling to promote the initial stage of B cell activation and expansion. Subsequently, EBV induces negative-regulatory factors of the TLR7 pathway, which are necessary for the establishment of latency.

Interactions of EBV with TLR9

In the primary infection, EBV initiates progressive lytic infection by expressing BZLF-1, which is the immediate-early lytic EBV gene and regulates the productive replication of EBV [204]. CpG oligodeoxynucleotide 2006 triggers innate immunity via the TLR9 of B cells to substantially inhibit BZLF-1 mRNA expression in acute EBV infection ex vivo and in Akata Burkitt lymphoma cells with latent EBV infection stimulated by anti-IgG. This reaction is mediated by IL-12 and IFN-γ [205]. When

triggering TLR9, B cells infected with EBV ex vivo efficiently transform by reducing the initiation of lytic EBV infection, and thereby reinforcing the maintenance of EBV latency [206].

The newly-formed EBV DNA in virus-infected cells contains an unmethylated CpG dinucleotide sequence. When the newly-formed virion is subsequently released, this dinucleotide is considered to be the main trigger of TLR9 [207]. After TLR9 recognizes EBV DNA, IRAK-1 and TRAF6 are activated by phosphorylation, thereby eliciting the IKK complex, resulting in NF-κB expression [180]. Subsequently, NF-κB promotes the production of inflammatory cytokines such as TGF-β, IL-6, IL-1, IL-23, and IL-21 [207]. These cytokines induce Th17 cells to secrete IL-17A, causing the recruitment of neutrophils and macrophages to infected sites and triggering the secretion of various pro-inflammatory mediators by various cell types. Salloum et al. treated mouse peripheral blood mononuclear cells with EBV DNA in the presence or absence of the TLR9 inhibitor oligodeoxynucleotide 2088, and showed that TLR9 inhibitors significantly decrease IL-17A production and play a crucial role in promoting IL-17A secretion [208] (Fig. 2).

Human cytomegalovirus

Interactions of HCMV with TLR2

Human cytomegalovirus (HCMV) is an important cause of disease in the immunodeficient host and the most common intrauterine infection in humans [209]. Acquired during early life, HCMV persists in a latent state for the life of the individual. Inflammatory cytokines can cause an innate immune response in the host. Through different effector cells (such as antigen-presenting cells [APCs], natural killer [NK] cells and

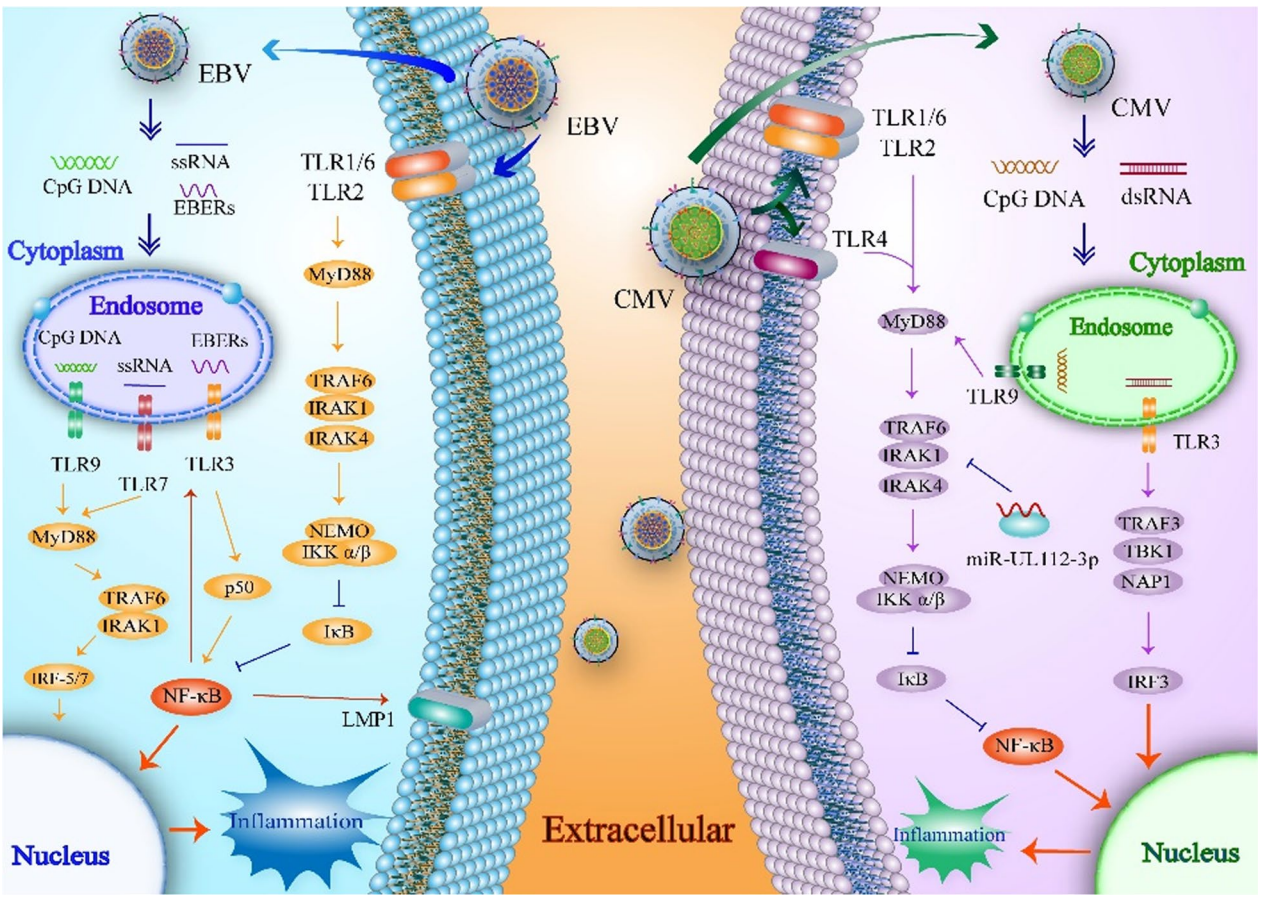

Fig. 2 Mechanism of responses of TLRs to EBV and HCMV**.** EBV activates the MyD88 pathway or the MyD88-independent pathway via the viral envelope and products. Upon EBV stimulation, TLR2, TLR3, TLR7, and TLR9 inside and outside the cells induce NF-κB or IRF-5/7 by a series of protein kinases to produce cyto-inflammatory factors. MyD88 recruits TRAF6 and IRAKs to activate the IKK complex composed of IKKα, IKKβ, and NEMO. Besides acting as an inflammatory mediator, NF-κB also upregulates the expression of LMP1 to trigger moderate inflammation. Similarly, HCMV reacts with TLRs, including TLR2, TLR3, TLR4, and TLR9, through the viral envelope or products. MyD88-NF-κB is the main pathway. However, dsRNA from CMV also activates IRF-3 and TLR3 to promote the expression of inflammatory factors. Meanwhile, the CMV-encoded miR-UL112-3p inhibits activation of the TLR2/NF-κB pathway, as well as the expression of various cytokines

phagocytes), anti-inflammatory cytokines, and IFNs respond to act against HCMV infection. The early release of IFN-I and other pro-inflammatory cytokines limits the spread of infection by establishing an "antiviral state" that triggers an efficient adaptive immune response to achieve latency and persistence [210]. To achieve latency, the HCMV-encoded US7 and US8 proteins impair the activation of TLR3 and TLR4 [211]. Similarly, the HCMV-encoded US9 protein reduces stimulator of interferon genes (STING) signaling and the production of IFN [212]. In addition, the HCMV tegument protein UL82 inhibits STING-mediated signaling to evade the antiviral immune response [213].

Generally, researchers have shown that TLRs 2–5 and TLR9 play crucial roles in the immune response to the activation of HCMV [50, 67, 214–217]. TLR2 recognizes the viral envelope glycoproteins gB and gH. Together with TLR1 or TLR6, TLR2 activates the MyD88-dependent and downstream transcription factor NF-κB signaling pathway to induce a series of pro-inflammatory cytokines, chemokines, and adhesion molecules, such as IL-6 and IL-8 [218–220]. MyD88 recruits TRAF6 and IRAKs to activate IKKα and IKKβ, together with NEMO, to form the IKK complex. IKKα triggers downstream NF-κB, while IKKβ phosphorylates the NF-κB inhibitor IκB, leading to its degradation [160, 161, 163]. This process results in the production of inflammatory cytokines. For example, IFN-γ stimulates a variety of innate immune cells and immune effector cells to develop the adaptive immune response and exert an antiviral effect [221]. MicroRNAs are small non-coding RNAs that cooperate with viral proteins to regulate the expression of viral and/or host genes, and they are involved in the immune evasion of infected cells, as well as the latency and reactivation of HCMV [222]. CMV-encoded microRNAs have also been shown to downregulate TLR2 expression [217]. Using an *in-silico* method, this study postulated that HCMV microRNAs trigger the TLR innate immune pathway; specifically, TLR2 might be a target for HCMV miR-UL112-3p. Because miR-UL112-3p is expressed after virus entry, downregulation of TLR2 occurs in the late stage of lytic infection. Immunoblot analysis of miR-UL112-3p-transfected cells revealed that it induces the reduction of endogenous TLR2 expression. The microRNA-mediated downregulation of TLR2 affects innate signal transduction, significantly inhibiting the activation of the IRAK1 and NF-κB pathways located in the TLR2/NF-κB signaling axis of the upstream kinase, as well as the expression of various cytokines such as IL-1β, -6, and -8. TLR2 protein levels decrease in the late stage of HCMV infection, and this is associated with the accumulation of miR-UL112-3p in fibroblasts and mononuclear THP1 cells.

Interactions of HCMV with TLR3, TLR4, and TLR5

TLR3 and TLR5 are also critical factors in the CMV infection pathway. TLR3 targets TRIF as a downstream adapter molecule instead of the adaptor protein MyD88 [149]. TLR3 activates the signaling complex assembled by TRIF. As a factor downstream to TRIF, TBK1 forms NAP1 and TRAF3 to elicit phosphorylation of the transcription factor IRF3, which produces inflammatory factors such as IFN-β [154–156, 221, 223]. CMV stimulates mast cells through the TLR3/TRIF signaling pathway to transmit effector functions. Subsequently, these cells release a large number of pro-inflammatory and antimicrobial mediators, many of which are stored in granules and released after degranulation, to enhance their protective properties and attract supplemental CD8 T cells to extravascular sites of viral replication [216]. During HCMV infection/reactivation, TLR5 plays an atypical role, probably because of the indirect effects of immunomodulation and immunostimulation on HCMV responses.

HCMV also promotes macrophage-mediated inflammatory responses through TLRs. HCMV infection stimulates cluster differentiation antigen 14 (CD14), TLR2, TLR4, and TLR5 on the surface to enhance the intracellular expression of the adaptor protein MyD88, and phosphorylation of IκB and NF-κB, thereby increasing the response of macrophages to viral components. The protein and mRNA levels of MyD88 are significantly elevated in macrophages. MyD88 combines with the cytoplasmic Toll/IL-1 region and triggers the phosphorylation of IRAK4, followed by the recruitment and phosphorylation of IRAK1, which then leads to the release of TNF-6 and transmission of the NF-κB signaling cascade [115, 224–228]. These mechanisms promote ligand-induced pro-inflammatory cytokine mRNA expression and the production of TNF-α, IL-6, and IL-8 proteins.

Interactions of HCMV with TLR9

TLR9, a pattern recognition receptor for HCMV in natural IFN-producing cells and DCs, recognizes unmethylated CpG motifs in viral DNA to initiate the transduction of intracellular signals by the adapter molecule MyD88, ultimately leading to the activation and transcription of NF-κB. Therefore, phosphorylated NF-κB encodes pro-inflammatory cytokines and chemokines, such as IFN-α and IL-12, to promote NK cells that recognize MCMV-infected cells by activating the receptor Ly49H [229, 230]. Ly49H interacts with the MCMV-encoded protein m157 on the surface of infected cells, resulting in elimination of the virus by NK cells [67] (Fig. 2).

Human herpesvirus-6 and -7

Interaction between HHV-6 and TLRs

HHV-6 causes the exanthema subtype; it preferentially infects functional immune cells and elicits various immunobiological changes [231–234]. Murakami et al. pointed out that HHV-6 infection significantly effects TLR4-induced cytokine levels [235]. This report revealed that TLR4 and the adaptor molecule MyD88 are significantly increased in HHV-6-infected cells. On the contrary, the phosphorylation levels of TAK-1, IKKα/β, and IκBα are reduced and affect the expression of NF-κB [236]. Therefore, upon stimulation of the TLR4 ligand, the ability of HHV-6-infected DCs to produce IL-10 and IL-8 is significantly impaired. This indicates that, in HHV-6-infected DCs, the disruption of TLR4 signaling is caused by a block in the downstream signaling pathway.

Interaction between HHV-7 and TLRs

HHV-6 and -7 participate in the pathogenesis of pityriasis rosea through TLRs. In HHV-7-positive cases, the expression levels of TLR2 and TLR4 are notably increased, while TLR9 and the HHV-7 viral load are positively correlated [237]. Interestingly, there is an interaction between HHV-6 and HHV-7: HHV-6 can be reactivated by HHV-7 infection [238].

Kaposi's sarcoma-associated herpesvirus

Kaposi's sarcoma-associated herpesvirus (KSHV), also named human herpesvirus-8, is well correlated with several forms of cancer such as Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease [239]. Like other herpesviruses, KSHV also causes latency in the host. During the latency, KSHV viral interferon regulatory factors (vIRFs) inhibit TLR3-mediated IFN induction [240]. Moreover, the replication and transcription activator (RTA) protein from KSHV triggers proteasomal degradation of the TLR3 adaptor protein TRIF, which blocks the subsequent pathway [241]. RTA also prevents TLR4 signaling via the degradation of MyD88 [242]. West et al. first reported that KSHV upregulates the TLR3 pathway during infection to induce TLR3-specific cytokines and chemokines such as IFN-1β and CXCL10 (IP-10) [243]. Furthermore, researchers have determined that TLR9 is the major receptor for KSHV. Once pDCs are infected, KSHV upregulates TLR9, CD83, and CD86, causing pDCs to produce IFN-α [244].

In addition, TLR4 plays an essential role in innate immunity to KSHV. KSHV microRNA clusters (particularly miRNA-K1, -K3, and -K11) trigger TLR4 with its co-receptors, CD14 and myeloid differentiation protein 2, to activate the MyD88-NF-κB pathway and produce IL-1β, IL-6, and IL-18 [245]. In addition, Lagos et al. found that KSHV suppression of TLR4 expression is the mechanism of immune escape during KSHV infection in endothelial cells [246]. Moreover, KSHV inhibits the TLR2 signaling pathway after infection in macrophages. In addition, the replication of KSHV and the transcriptional activator RTA/ORF50 block the TLR2 and TLR4 signaling pathways via reducing the expression of functional proteins. Moreover, KSHV-encoded microRNAs reduce the inflammatory factor expression by modulating two components of the TLR/IL-1R pathway, IRAK1 and MyD88 [247]. Thus, KSHV uses two mechanisms to avoid attack by the host immune system, leading to repeated infection in the host [248].

Conclusions

To date, studies have shed light on the interactions between TLRs and herpesviridae infections, especially the subsequent signaling pathways. Research continues to reveal new insights into TLR pathways and their roles in host defense responses, especially in innate immunity [249–251]. However, the detailed mechanisms of mutual action between HSV RNA and TLR3 remain unclear [138–140, 148]. Moreover, understanding the mechanisms of activation and regulation in detail will help in the design of efficient vaccines and therapeutics based on modulating the TLRs more precisely. In this context, the use of TLR antagonists and regulators such as MPL, topical SMIP-7.7, Annexin A2, ubiquitin ligase TRIAD3A, pathogenesis-related protein from *Oenanthe javanica*, and RP105 might have broader applications [29, 31, 32, 252–254]. Although computer-assisted screening of TLR regulators is plausible, the rational design of selective TLR modulators still faces enormous challenges and studies are few. Furthermore, there are some new developments in anti-viral targeting of the host factors involved in TLR signaling. BX795, an inhibitor TBK1, potently suppresses multiple strains of HSV-1, including an ACV-resistant HSV-1 strain. BX795 targets Akt and blocks viral protein synthesis by reducing Akt phosphorylation in infected cells, but a more precise antiviral mechanism requires further investigation [255]. Therefore, clarifying the interaction between each TLR and the associated virus is critical for controlling the development of the diseases caused by the herpesviruses.

Abbreviations

TLRs: Toll-Like receptors; HSV-1,-2: Herpes simplex virus type 1 and 2; VZV: Varicella zoster virus; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; HHV-6, -7: Human herpesvirus 6 and 7; KSHV: Kaposi's sarcoma-associated herpesvirus; PRRs: Pathogen recognition receptors; MyD88: Myeloid differentiation 88; TRIF: Toll/IL-1R(TIR)-domain-containing adaptor protein; TIRAP: TIR-domain-containing adaptor protein; TRAM: TRIF-related adaptor molecule; CpG: Cytosine-phosphate-guanine; PI3K: Phosphatidylinositol 3-kinase; TRAF: Tumor-necrosis-factor-receptor-associated factor; IRAK1: Interleukin-1 receptor-associated kinase 1; MAPKs: Mitogen-activated protein kinases; Akt (PκB): Protein kinase

B; JNK: Jun N-terminal kinase; NAP1: NAK-associated protein 1; TBK1: Tumor-necrosis-factor receptor-associated factor (TRAF) family-member-associated NF-κB activator (TANK) binding kinase 1; TAK-1: Transforming growth factor-β (TGF-β)-activated kinase 1-related kinase; IKK: Inhibitor of NF-κB kinase; NF-κB: Nuclear factor-κB; TNF: Tumor-necrosis factor; IRF: Interferon regulatory factor; IFN: Interferon, CD14: cluster differentiation antigen 14; LMP1: EBV latent membrane protein 1; NEMO: IKK receptor protein IKKγ; pDCs: PlaSmacytoid dendritic cells; IL: Interleukin; PMC: Peripheral blood mononuclear cells; RIP1: Receptor interacting protein 1; LRRs: Leucine-rich repeats; UNC-93B: Unc-93 homolog B1; AP-1: Activator protein-1; APC: Antigen-presenting cells; NK: Natural killer; dsRNA: Double-stranded RNA; ssRNA: Single-stranded RNA; EGFR: Epidermal growth factor receptor; ERK: Extracellular receptor kinase; STING: Stimulator of interferon genes.

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WZ, QX, YZ, XE, WG, MZ, WZ, RR and ZL organized the content of the entire manuscript and wrote the manuscript. All authors have read and approved the final manuscript.

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